Personalizing, not patronizing: the case for patient autonomy by unbiased presentation of management options in stage I testicular cancer

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Abstract: Testicular cancer (TC) is the most common neoplasm in males aged 15-40 years. The majority of patients have no evidence of metastases at diagnosis and thus have clinical stage I (CSI) disease [Oldenburg J, Fossa SD, Nuver J et al. Testicular seminoma and non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24(Suppl 6): vi125-vi132; de Wit R, Fizazi K. Controversies in the management of clinical stage I testis cancer. J Clin Oncol 2006; 24: 5482-5492.]. Management of CSI TC is controversial and options include surveillance and active treatment. Different forms of adjuvant therapy exist, including either one or two cycles of carboplatin chemotherapy or radiotherapy for seminoma and either one or two cycles of cisplatin-based chemotherapy or retroperitoneal lymph node dissection for non-seminoma. Long-term disease-specific survival is 99% with any of these approaches, including surveillance. While surveillance allows most patients to avoid additional treatment, adjuvant therapy markedly lowers the relapse rate. Weighing the net benefits of surveillance against those of adjuvant treatment depends on prioritizing competing aims such as avoiding unnecessary treatment, avoiding more burdensome treatment with salvage chemotherapy and minimizing the anxiety, stress and life disruption associated with relapse. Unbiased information about the advantages and disadvantages of surveillance and adjuvant treatment is a prerequisite for informed consent by the patient. In a clinical scenario like CSI TC, where different disease-management options produce indistinguishable long-term survival rates, patient values, priorities and preferences should be taken into account. In this review, we provide an overview about risk factors for relapse, potential benefits and harms of adjuvant chemotherapy and active surveillance and a rationale for involving patients in individualized decision making about their treatment rather than adopting a uniform recommendation for all.

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Testicular cancer (TC) is the most common neoplasm in males aged 15–40 years. The majority of patients have no evidence of metastases at diagnosis and thus have clinical stage I (CSI) disease [Oldenburg J, Fossa SD, Nuver J et al. Testicular seminoma and non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24(Suppl 6): vi125–vi132; de Wit R, Fizazi K. Controversies in the management of clinical stage I testis cancer. J Clin Oncol 2006; 24: 5482–5492.]. Management of CSI TC is controversial and options include surveillance and active treatment. Different forms of adjuvant therapy exist, including either one or two cycles of carboplatin chemotherapy or radiotherapy for seminoma and either one or two cycles of cisplatin-based chemotherapy or retroperitoneal lymph node dissection for non-seminoma. Long-term disease-specific survival is ~99% with any of these approaches, including surveillance. While surveillance allows most patients to avoid additional treatment, adjuvant therapy markedly lowers the relapse rate. Weighing the net benefits of surveillance against those of adjuvant treatment depends on prioritizing competing aims such as avoiding unnecessary treatment, avoiding more burdensome treatment with salvage chemotherapy and minimizing the anxiety, stress and life disruption associated with relapse. Unbiased information about the advantages and disadvantages of surveillance and adjuvant treatment is a prerequisite for informed consent by the patient. In a clinical scenario like CSI TC, where different disease-management options produce indistinguishable long-term survival rates, patient values, priorities and preferences should be taken into account. In this review, we provide an overview about risk factors for relapse, potential benefits and harms of adjuvant chemotherapy and active surveillance and a rationale for involving patients in individualized decision making about their treatment rather than adopting a uniform recommendation for all.

Key words: testicular cancer stage I, active surveillance, adjuvant chemotherapy, seminoma, non-seminoma, risk factors

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introduction

Testicular cancer (TC) is the most common neoplasm in young males aged between 15 and 40 years, and the majority of patients are diagnosed with clinical stage I (CSI) disease, meaning that they have no evidence of regional or distant metastases [1, 2]. Active surveillance (AS) is an option for CSI TC patients, but the authors of this article are not convinced that 'most CSI TC patients should be encouraged toward AS as primary management' as recently proposed by Nichols et al. [3] Rather, each patient should be informed about the potential advantages and disadvantages of AS and adjuvant chemotherapy (ACT) as a prerequisite for obtaining informed consent for either. Here, we present our arguments for a personalized approach to management [4].

seminoma

About 80%–85% of patients with seminoma are diagnosed with CSI and ∼16% relapse during AS [5]. Enthusiasm for adjuvant radiotherapy has been tempered by the risk of radiation-induced secondary cancers and most European guidelines have removed this treatment option [1, 6]. Tumor size >4 cm and invasion of the rete testis were associated with an increased risk of relapse in an international retrospective study of 638 men, reporting relapse rates of 31.5%, 15.9% and 12% in those with both, one and neither risk factor, respectively [7]. Some subsequent reports questioned these findings [5, 8], but more recently, SWENOTECA reported that the presence of either risk factor independently increases the risk of relapse during AS significantly [9]. SWENOTECA reported a relapse rate of 2.9% in patients without risk factors compared with 21.7% in patients with 1–2 risk factors, although the number of men with two risk factors who were managed with surveillance was too small to assess whether their risk of relapse was higher than those with only one [9]. There are thus abundant data confirming our ability to identify low- and intermediate-risk patients, but fewer than one-third of the 'high-risk' patients are expected to relapse if managed with surveillance. For patients weighing AS versus ACT, knowing our best estimate of their risk of relapse is critical for them to be able to make an informed decision.

A single cycle of adjuvant carboplatin (AUC7) has been established as effective ACT when compared with adjuvant radiotherapy in the largest TC phase III trial ever reported. Relapse rates were similar, but carboplatin resulted in fewer adverse effects, less sick-leave and a significant reduction in contralateral testicular tumors [10, 11]. Relapse rates after a single dose of adjuvant carboplatin in unselected populations are 4%, translating into a 75% relapse reduction [5], which is acceptable to many patients given the low risk of complications. The prospect of a single infusion with a high chance of being able to work shortly thereafter is appealing to many patients and unique in cancer treatment. There is, however, skepticism against carboplatin, mainly in the USA, where adjuvant radiotherapy still is considered a viable option for CSI seminoma [12]. In numerous studies, two cycles of carboplatin reduced the relapse rate to 0%–3%, translating into an average relapse reduction of 90%, but this approach has not been tested in a randomized, controlled trial [10, 13, 14].

non-seminoma

About 55%–60% of patients with non-seminoma TC present with CSI. Approximately 25%–30% relapse during AS. Relapse rates depend on lympho-vascular invasion (LVI) in the primary tumor: 50% in LVI+ versus 15% in LVI− patients [15–17]. Thereby, most guidelines differentiate the treatment of high- and low-risk patients based on LVI status. A predominance of embryonal carcinoma in the primary tumor also appears to be associated with an increased risk of relapse, but this variable has been less well validated and appears to be a less powerful prognostic factor [18].

Historically, retroperitoneal lymph node dissection (RPLND) has been a standard treatment option, but given inferior outcomes in a community-based, randomized trial [19], RPLND is no longer regarded as standard in the community setting [1, 6]. RPLND is, however, associated with the lowest likelihood of requiring systemic chemotherapy when carried out by highly experienced surgeons. The downside of RPLND is that it is associated with the highest likelihood of requiring more than one treatment modality because of the number of patients who receive chemotherapy after RPLND either for pathological stage II disease discovered during the operation or for relapse.

ACT in stage I non-seminoma

ACT with two cycles of bleomycin, etoposide and cisplatin (BEP) has been employed in many smaller series, but the two largest studies used BEP × 1. In a randomized trial comparing RPLND and BEP × 1, 191 patients received ACT with a reported 2-year relapse rate of 0.5% [19]. In a community-based prospective study, high-risk patients were recommended BEP × 1, whereas low-risk patients could choose between AS and BEP × 1 [20]. Relapse rates after a median follow-up of 7.9 years of 517 patients who received BEP × 1 were 1.6% and 3.2% for LVI−, and LVI+ tumors, respectively, whereas relapse rates during surveillance were 12% and 42% [17]. Thereby, ACT prevented >90% of relapses. Importantly, no relapses were observed after 3.3 years. Results of a completed UK prospective trial, of BEP × 1 in 246 high-risk patients, are eagerly awaited. Many European experts consider BEP × 1 as the new standard ACT for non-seminoma, since reducing BEP to one cycle is expected to improve the risk–benefit ratio considerably.

burden of intervention

Quantifying the overall 'treatment burden' can be helpful for decision making (Table 1). As an example, 100 LVI+ patients managed with AS will receive ∼*150 cycles of BEP*, as ∼50% will relapse, requiring minimum BEP × 3 with additional RPLND in those with residual lesions. BEP × 1 for 100 patients equals 100 cycles of BEP, and subsequently approximately nine additional BEP cycles for ∼3 (3.2%) relapsing patients, adding up to a total of *109 cycles of BEP*. Furthermore, only three men treated with AC will end up needing a full course of 3–4 cycles of chemotherapy, compared with 50 high-risk men undergoing AS (Table 1). Thus, while both the short and long-term toxicities of chemotherapy must be taken into consideration when making treatment decisions, administering ACT to patients LVI reduces the

Table 1. Estimated use of BEP cycles for different scenarios of AS versus adjuvant BEP × 1 in relation to vascular invasion

	All		VI+		VI−	
	AS	ACT	AS	ACT	AS	ACT
No. of patients	100	100	100	100	100	100
Relapses	25	2	50	3	15	2
No. of BEP cycles	75	106	150	109	45	106

Salvage treatment = 3–4 × BEP ± surgery.
VI, vascular invasion; +, present; −, absent; AS, active surveillance; ACT, adjuvant chemotherapy (BEP × 1); BEP, bleomycin, etoposide and cisplatin.

overall chemotherapy exposure in this population. Also, RPLND might be necessary in as many as 26% of patients relapsing during AS [21]. This number is higher than that reported by SWENOTECA, where 7.7% of AS patients required RPND as opposed to 2.2% after ACT [20]. Nevertheless, these numbers favor ACT both with regard to chemotherapy and surgery [22]. The financial costs of managing non-seminoma CSI have been calculated by Link et al. [23] who concluded that ACT is cost effective over AS or RPLND in LVI+ non-seminoma CSI patients. Of note, these calculations were based on BEP × 2, suggesting an even bigger advantage of BEP × 1.

toxicity related to ACT versus relapse treatment

Treatment-related toxicity is crucial considering survival rates of 99%–100% regardless of treatment strategy. So far, there is little indication that adjuvant carboplatin is associated with serious late toxicities [24]. Admittedly, long-term data exceeding 15 years are lacking. Most serum parameters as well as lung function, audiometry, sexual function and fertility rates seem to be unaffected by adjuvant treatment with 1–2 cycles of BEP, although the numbers are small and observation time is too short for definitive conclusions [25–27].

Relapse treatment is, however, associated with considerable long-term toxicity including serious late effects like cardiovascular disease and second cancers [28]. Of note, acute toxicity is also an issue following chemotherapy for metastatic disease: the single death from acute toxicity among 745 CSI patients in the SWENOTECA report was initially managed by AS, relapsed, and then received four cycles of BEP with subsequent brain herniation secondary to a stroke 1 week after the last cycle [20]. A clear dose–relationship has been established for the following BEP sequelae: pulmonary toxicity, fertility, neurotoxicity, ototoxicity, nephrotoxicity, metabolic syndrome and hypogonadism [29–35]. Considering these well-known toxicities after BEP × 3–4, it appears reasonable to administer ACT to reduce the risk of relapse and thereby limit the proportion of patients requiring such extensive chemotherapy. However, we do not recommend administering ACT to all CSI TC patients. Instead, we favor discussing the advantages and disadvantages of this option as well as those of AS. The use of AS, thus avoiding unnecessary chemotherapy in the majority of patients, is very appealing. However, there are challenges to this approach.

challenges of AS

Potential disadvantages of AS include secondary malignancies from ionizing radiation from imaging studies, non-adherence to the surveillance schedule and consequent presentation with poor-risk disease, the toxicity of 3–4 cycles of BEP, resection of residual masses and the life disruption associated with relapse. Radiation exposure by frequent CT examinations during AS is a concern in patients with cure rates approaching 100% [36]. Imaging by MRI avoids this risk, but is unavailable for the majority of patients worldwide. However, radiologic follow-up of TC patients in Sweden and Norway is based on MRI with excellent results [5, 17, 37]. Lifetime cancer attributable to CT examinations for patients with CSI non-seminoma has been calculated to range from 1 in 52 (1.9%) to 1 in 63 (1.2%), depending on age [38]. It is not currently possible to substantiate the risk of cancer induction by radiation exposure, but it is certainly not zero and radiation exposure can be reduced if ACT is chosen rather than AS according to the guidelines from the National Comprehensive Cancer Network (NCCN) or the Royal Marsden Hospital, London (Table 2) [39].

Successful AS requires adherence to the follow-up schedule, but a significant proportion of patients do not adhere to recommended follow-up [41]. Excellent outcomes for AS are reported by countries with a well-funded public healthcare system, e.g. Scandinavian countries and Canada. However, except from the work by Nichols et al. who cooperates with Canadian institutions, there are no United States-based reports on long-term outcomes or adherence with AS. Thereby, data from Yu et al. assessing adherence rates by insurance claims are of particular interest: 29% of patients were not assessed for recurrence at all. Adherence to follow-up declined with time, and only 45% of patients underwent abdominal imaging during later years of AS [42]. A Canadian series reported a mean rate of 'compliance' with CT scanning of only 64% (range 32.2%–100%) [43]. 'Lost to follow-up' is unfortunately an all too frequent status among the young and mobile CSI TC patients [44].

Low adherence was presumably the reason for the poor survival of only 90% of 145 CSI non-seminoma patients, managed at the Slovakian center in Bratislava from 1984 to 1991 with AS

Table 2. Number of CT scans required for CSI TC during AS or after ACT

	Seminoma		Non-seminoma	
	AS	ACT	AS	ACT
Royal Marsden Hospital [39]	7	3	3	1
NCCN [40]	7–8	3	8–12	6–7

CSI, clinical stage I; TC, testicular cancer; AS, active surveillance; ACT, adjuvant chemotherapy; NCCN, National Comprehensive Cancer Network.

independent of LVI status: 52 of 145 (36%) patients experienced a relapse, and 15 of these (29%) died from TC [45]. Admittedly, these figures may not apply for contemporary patients managed in European or American centers, but the follow-up protocol was standardized, including repeated CT imaging and relapse treatment comprised cisplatin-based chemotherapy. This center applied a risk-based treatment from 1992 onwards with AS reserved for LV− patients only, whereas LVI+ patients received ACT with BEP × 2. Subsequently, only 2 of 111 (1.9%) LVI+ patients relapsed and neither of them died [45].

Patients may experience increased anxiety before follow-up visits over many years. Fear of relapse has been reported by approximately one of three long-term survivors 10 years after successful treatment [46]. Personality qualities like coping ability and level of distress are important factors for fear of relapse and should be incorporated into decision making in CSI TC.

The resulting disruption of normal life by recurrence during AS, necessitating 9–12 weeks of intensive chemotherapy and possibly surgery at an unplanned time point, is likely to be particularly damaging for adolescent and young adult males who are establishing their lives as the diagnosis of metastatic disease sets almost all activities including work and education at an abrupt halt. In contrast, if ACT is chosen as elective therapy, the likelihood of having their life interrupted again—after the time of diagnosis—is reduced to <4%. This peace of mind is of considerable value for some individuals and might have contributed to the following results: in a British study, patients tended to opt for AS if the risk of recurrence was <30%, while the majority opted for ACT if the risk approximated 50%. Importantly, there was wide variation among apparently similar groups [47]. These figures pertain to BEP × 2 as ACT and BEP × 4 as treatment of recurrence. Probably, a greater proportion of patients would have chosen ACT if BEP × 1 had been an option. These figures help to estimate the threshold level for the overall cohort of patients. The individual threshold for choosing ACT or AS, however, may be different, and is influenced by psychological factors such as personal risk aversion.

unbiased information

Providing unbiased information is essential and is mandated by the ethical mandate to respect patient autonomy, which is defined as ‘the right of patients to make decisions about their medical care without their health care provider trying to influence the decision. Patient autonomy does allow for health care providers to educate the patient but does not allow the health care provider to make the decision for the patient’[48].

The following statement by Nichols et al. [3] may infringe the principle of patient autonomy and unbiased information: ‘Clinical outcomes using a broad policy of active surveillance for clinical stage I testicular cancer are unsurpassed by management strategies that rely on adjuvant therapies’. We consider this statement to be biased in favor of AS since there are no trials comparing AS with ACT allowing this conclusion to be drawn. Intriguingly, it has equal veracity when the terms ‘active surveillance’ and ‘adjuvant therapies’ are switched.

Open and honest communication about all management options may contribute to achieving an effective doctor–patient relationship, which has been shown to predict adherence to follow-up schedules [41]. The authors of the ‘Prospective Study of Factors Predicting Adherence to Medical Advice in Men With Testicular Cancer’ did conclude that ‘Patients who perceived an unsatisfactory affective relationship with their clinician that included an inability to trust the clinician and a perception that they were not being treated as “a person” were subsequently more likely to disregard medical advice regarding follow-up’. The most relevant way of personalizing management of CSI TC is the presentation and appraisal of risk factors and their implications on the potential benefit of ACT versus AS.

In their editorial on the risk-adapted management of nonseminoma CSI by SWENOTECA, which recommends ACT to patients with LVI+, and leaves the decision between AS and ACT to LVI− patients, Nichols and Kollmannsberger [49] have expressed their skepticism toward patient autonomy: ‘Is patient autonomy in treatment decisions a good thing, or does it just shift the burden of the wrong choice to the patient with associated remorse and guilt?’ However, both AS and ACT for CSI TC result in nearly 100% long-term disease-specific survival and neither has been shown to result in superior quality of life, so it is unclear how either option could be considered ‘wrong’. Moreover, what is right for one patient may not be for the next. Most patients appreciate comprehensive information and accept uncertainty and are willing to contribute to decision making about their own health. We therefore refute attempts to ‘protect’ them from this uncertainty by patronizing them and denying them self-determination. Allowing patients to decide on either ACT or AS according to their own preferences gives empowerment and respects them as self-determining individuals; this, in turn, strengthens the therapeutic relationship and can increase adherence with either self-chosen approach.

A recent decision analysis revealed that quality-adjusted survival was similar for AS, ACT and RPLND. Adjuvant treatment was favored when the risk of recurrence was 37% or higher [50]. Of note, in the absence of reliable long-term assessment, toxicity data after BEP × 3 were presented instead of BEP × 1, thereby overestimating ACT’s toxicity. Furthermore, the complications of AS might have been underestimated since up to one of four relapsing patients requires post-chemotherapy RPLND and 5.4% have intermediate or even poor prognosis according to IGCCCG [21].

Within SWENOTECA, 93% of the LVI+, and approximately 1 in 3 LVI−, patients received ACT, with the remainder following AS [20]. Within the British Columbia Cancer Agency or the Oregon Testis Cancer Program both of which follow a non-risk-adapted surveillance program, 223 of 233 (95%) CSI non-seminoma patients did opt for AS, including 60 LVI+ patients, of whom 30 (50%) experienced a relapse [18]. The reasons for this diametrically different pattern of choice of LVI+ patients are possibly not based on different risk perceptions by the patients, but rather varying risk presentation by the physicians.

Few, if any, situations within oncology are characterized by such a high degree of clinical equipoise between the alternatives, e.g. AS versus ACT for CSI TC [51]. Clinical equipoise, defined ‘as genuine uncertainty within the expert medical community about the preferred treatment’ is considered an ethical requirement for randomized trials, and mandates in the setting of TC CSI unbiased information about the benefits and risks of each alternative in order to let the patient reach an individual decision.

conclusion

We encourage tailoring management of CSI TC according to the patient's individual risks and his individual interpretation of these risks. Many patients consider ACT a lesser evil than the prospect of frequent follow-up visits with the risk of requiring BEP × 3–4 at an unplanned time point plus potential additional surgery. The reported low adherence to AS protocols could indicate an evasion strategy by a substantial proportion of patients and dealing with their TC with ACT might be safer. Considering very similar outcomes of AS and ACT, individual patient preferences should be a strong factor in management decision. Therefore, we believe in:

(1) Identifying the patient's individual risks and preferences,
(2) Involving the patient in a discussion about the potential trade-offs of the different management strategies and
(3) Helping the patient in deciding which management suits him.

disclosure

The authors have declared no conflicts of interest.

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Available evidence and new biological perspectives on medical treatment of advanced thymic epithelial tumors

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Thymic epithelial tumors (TETs) are rare primary mediastinal tumors arising from thymic epithelium. Their rarity and complexity hinder investigations of their causes and therapy development. Here, we summarize the existing knowledge regarding medical treatment of these tumors, and thoroughly review the known genetic aberrations associated with TETs and the present status of potential biological treatments. Epidermal growth factor receptor (EGFR), stem-cell factor receptor, insulin-like growth factor-1 receptor (IGF1R), and vascular endothelial growth factors (VEGF-A, VEGF-B, and VEGF-2) are overexpressed in TETs. EGFR overexpression in TETs is associated with higher stage, and IGF1R overexpression has poor prognostic value. Data indicate that anti-IGF1R monoclonal antibodies, and inhibitors of angiogenesis, somatostatin receptors, histone deacetylase, mammalian target of rapamycin, and cyclin-dependent kinases may be active against TETs. Continued investigations in this field could lead to advancement of targeted and biological therapies for TETs.
Key words: thymic epithelial tumors, thymoma, thymic carcinoma, chemotherapy, biological agents, targeted therapy

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